REMARKS

Claims 1-18 are pending in the subject application. Claims 11-17 are withdrawn from consideration as being drawn to non-elected inventions. Applicants have hereinabove amended claim 1 and canceled claims 2 and 8-10 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in the future. Support for the amendment to claim 1 may be found in the specification, *inter alia*, at page 3, lines 1-2; page 5, second and third full paragraph; page 6, first full paragraph; page 7, middle full paragraph; page 8, middle full paragraph; and the paragraph bridging pages 9 and 10 as well as by the Examples. Upon entry of this Amendment, claims 1, 3-7, and 18 will be pending and under examination.

Information Disclosure Statement

Applicants acknowledge that the listing of references in the specification is not a proper information disclosure statement under 37 C.F.R. §1.98(b). Accordingly, applicants intend to prepare and file an information disclosure statement so that the references can be considered by the Examiner.

Specification

Title

The Examiner objected to the title of the subject specification because the title of the invention is not descriptive. The Examiner stated a new title is required that is clearly indicative of the invention to which the claims are directed.

In response, applicants note that the title has been amended hereinabove and now recites "Tissue Amyloid Plaque Immunoreactive Assay". Applicants maintain that the title, as amended, is descriptive of the claimed invention. Accordingly, applicants respectfully request the Examiner withdraw this ground of objection.

Embedded Hyperlink

The Examiner objected to the disclosure of the subject specification because it contains an embedded hyperlink and/or other form of browser-executable code at page 13. The Examiner stated that applicants are required to delete the embedded hyperlink and/or other form of browser-executable code.

In response, applicants note that the specification has been amended hereinabove to remove the embedded hyperlink. Accordingly, applicants respectfully request that the Examiner remove this ground of objection.

Rejection Under 35 U.S.C. §112

The Examiner rejected claims 1-10 and 18 under 35 U.S.C. §112, first paragraph, as allegedly failing to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Specifically, the Examiner asserted that the specification, while being enabling for detecting an increased level of immunostaining on brain sections of $APP^{SW}xPS1^{M146L}$ double-transgenic mice or increased levels of antibodies against β-amyloid in serum and CSF samples of Alzheimer disease (AD) patients who are immunized with Aβ peptides, AN1792(Qs-21), and detecting a positive correlation between the increased immunostaining and improvement of immunization treatment in AD patients, does not reasonably provide enablement for a method of monitoring an immunotherapy in a subject suffering from an amyloidogenic disease or a neurodegenerative disease associated with abnormal protein aggregates by contacting all types of test samples with all forms of amyloid plaque or abnormal protein aggregates-containing samples and comparing the level of immunoreactivity to an unknown reference value that represents a undefined disease or undefined health status as broadly claims. The Examiner alleged that one of skill in the art would be required to perform undue experimentation to practice the claimed invention as it pertains to a method of monitoring an immunotherapy in a subject suffering from an

amyloidogenic disease or a neurodegenerative disease associated with the deposition of abnormal protein aggregates.

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection, applicants note that claims 8-10 have been canceled, thus rendering moot the Examiner's rejection with respect to claims 8-10. Applicants note further that claim 1 has been amended, thereby obviating the Examiner's ground of rejection.

The Examiner noted on page 6 of the August 17, 2007 Office Action that applicants are enabled for monitoring an immunotherapy in patients suffering from AD by obtaining test samples from patients immunized with Aβ1-42 and detecting generation of anti-Aβ antibodies; in particular generation of antibodies that can be detected by an increased immunostaining on brain sections containing human amyloid-plaque or using brain sections of $APP^{SW}xPS1^{M146L}$ when compared to controls without generation of such antibodies. Applicants maintain that the specification is enabling for the method as recited in amended claim 1.

Accordingly, applicants maintain that the Examiner's ground of rejection has been overcome and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-10 and 18 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleged that claims 1-10 and 18 are indefinite because applicants recite "a reference value representing a known disease or health status, or representing the status of prior to onset of said immunotherapy in claims 1 and 8. The Examiner further alleged that the disclosure fails

to set forth the metes and bounds of what is encompassed within the definitions of such a reference value, a known disease, health status, and the status of prior to onset of said immunotherapy.

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection, applicants note that claims 8-10 have been canceled thus rendering moot the Examiner's ground of rejection with respect to claims 8-10. Applicants note further that claim 1 has been amended to recite, in relevant part, "comparing said level of immunoreactivity to (i) a reference level of immunoreactivity representing Alzheimer's disease, or (ii) a level of immunoreactivity determined prior to onset of said immunotherapy in said subject". Applicants maintain that a person of ordinary skill in the art would understand the metes and bounds of what is encompassed in a reference level of immunoreactivity representing Alzheimer's disease and a level or immunoreactivity determined prior to the onset of said immunotherapy.

In view of these remarks, applicants maintain that as amended, claim 1, and the claims which depend therefrom, satisfy the requirements of 35 U.S.C. §112, second paragraph. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejections under 35 U.S.C. §102

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 1-4, 8 and 18 under 35 U.S.C. §102(b) as allegedly being anticipated by Dodel et al. (EP1172378, published January 16, 2002). Specifically, the Examiner asserted that Dodel et al. teach a method of monitoring an immunotherapy in a subject suffering from AD, teach AD patients administered with an anti-Aβ-antibody, and detection of the levels of anti-Aβ antibodies and Aβ peptides in plasma and CSF as compared to controls or before treatment. The Examiner further asserted that Dodel et al. teach that AD patients

treated with anti-Aβ antibodies show reduced Aβ burden in the brain of AD patients, which is an inherent result of an increased level of immunoreactivity and a positive outcome.

In response, applications respectfully traverse the Examiner's ground of rejection. Applicants note that claim 1 has been amended hereinabove.

Applicants note that Dodel et al. teach the detection of the levels of anti-Abeta antibodies utilizing an ELISA assay, i.e. detection of antibody binding to artificial synthetic Abeta peptide immobilized on a plastic plate. In contrast, the method of claim 1 provides, in relevant part, for obtaining a test sample from the subject and contacting said test sample with a tissue section containing β-amyloid plaque. Dodel et al., therefore, do not recite every element of applicants method as recited in claim 1. Accordingly, applicants maintain that claim 1, and the claims which depend therefrom, are not anticipated by Dodel et al.

For the reason stated above, applicants maintain that Dodel et al (EP. EP1172378, published January 16, 2002) do not disclose each and every element of applicants' invention and therefore does not anticipate applicants' invention.

In view of these remarks, applicants maintain that claim 1 and the claims which depend therefrom, satisfy the requirements of 35 U.S.C. §102(b). Accordingly, applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

Rejections Under 35 U.S.C. §102(e)

The Examiner rejected claims 1-10 and 18 under 35 U.S.C. §102(e) as allegedly being anticipated by Schenk et al. (U.S. Patent No. 6,787,523 published September 7, 2004, priority December 2, 1997). Specifically, the Examiner alleged that Schenk teaches a method of monitoring an immunotherapy in a subject suffering from an amyloidogenic disease or a

neurodegenerative disease associated with an abnormal protein aggregates, and teaches immunizing patients with AD or a transgenic animal model of AD, PDAPP, with Aβ peptides including AN1792. The Examiner further alleged that Schenk teaches a method of detecting the level of antibodies in serum and CSF after immunization with AN1792 by ELISA and also by an immunohistochemical method using brain sections of PDAPP transgenic mice or AD patient brain sections as compared to controls. The Examiner also alleged that Schenk teaches detection of an increased level of immunoreactivity on brain sections by contacting the sections with serum or the CSF containing anti-Aβ antibodies from animals that show increased clearance of Aβ burden, which is indicative of improvement of clinical outcomes.

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection, applicants note that claims 8-10 have been canceled, thus rendering moot the Examiner's rejection with respect to those claims. Applicants note further that claim 1 has been amended hereinabove and address the Examiner's comments as they may apply to claim 1.

Applicants respectfully disagree with the Examiner's allegation that claim 1 is anticipated by Schenk et al (US '523). Applicants note that Schenk (US'523) teach the measurement of antibody titers by sandwich ELISA, i.e. detection of antibody binding to artificial synthetic Abeta peptide immobilized on a plastic plate. In contrast, applicants claimed method provides, in relevant part, for obtaining a test sample from the subject and contacting said test sample with a tissue section containing β-amyloid plaque.

The Examiner asserted on page 11 of the August 17, 2007 Office Action that Schenk et al. teach a method of detecting the levels of antibodies in serum and CSF after immunization with AN1792 by ELISA and also by an immunohistochemical method using brain section of PDAPP transgenic mice or AD patient brain sections as compared to controls. Schenk et al.

disclose a method where Aβ plaques in AN1792 treated brains were coated with endogenous IgG. The results showed that immunization with a synthetic Abeta protein generates antibodies that recognize and bind in vivo to the Abeta in amyloid plaques"; see Schenk in col. 28, lines 7-20 and col. 32 lines 21-3. Schenk et al., however, do not teach applicants method as recited in claim 1. Specifically, Schenk et al do not teach the following elements of applicants claimed invention: obtaining a test sample from the subject, contacting said test sample with a tissue section containing β-amyloid plaque, determining the level of immunoreactivity of said test sample with β-amyloid plaques present in said amyloid plaque-containing tissue section. Accordingly, applicants maintain that claim 1, and the claims which depend therefrom, are not anticipated by Schenk (US '523) et al.

For the reason stated above, applicants maintain that Schenk et al. (U.S. Patent No. 6,787,523) do not disclose each and every element of applicants' invention and therefore do not anticipate applicants' invention.

In view of these remarks, applicants maintain that claim 1 and the claims which depend therefrom, satisfy the requirements of 35 U.S.C. §102(e). Accordingly, applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

Rejections under 35 U.S.C. §103

The Examiner rejected claims 1-10 and 18 under 35 U.S.C. §103(a) as allegedly being unpatentable over Dodel et al (EP 1172378) in view of Schenk et al (Nature. 1999. 400:173-177). Specifically, the Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use brain sections of transgenic animals containing amyloid plaques as a tool to detect the antibody level of immunization and the immunoreactivity of immunogens and antibodies against immunogens. The Examiner further alleged that the person of ordinary kill in the art would have been motivated to do so because animals immunized with Aβ generate the anti-Aβ antibodies

against Aβ plaques and show reduced Aβ burden or increased clearance, which is an increased level of immunoreactivity of antibodies against Aβ, as taught by Schenk et al. The Examiner also alleged that one of ordinary skill in the art would have expected success in monitoring an immunotherapy in a subject suffering from AD by obtaining test samples from patients immunized with Aβ, detecting an increased level of immunoreactivity between the antigen and an antibody on brain sections of transgenic animals that have the same epitopes as immunogens of immunization, and using the increased immunoreactivity as an indicator of improvement of the immunotherapy in AD.

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection, applicants note that claims 8-10 have been canceled, thus rendering moot the Examiner's rejection with respect to those claims. Applicants have hereinabove amended claim 1 and address the Examiner's comments as they may apply to claim 1.

Applicants respectfully disagree with the Examiner and maintain that Dodel et al., alone or in combination with Schenk et al., do not render obvious applicants invention as recited in claim 1. Specifically, applicants maintain that Dodel et al. in combination with Schenk et al. do not teach each and every element of applicants' invention as recited in claim 1.

Dodel et al. teach the detection of the levels of anti-Abeta antibodies utilizing an ELISA assay, i.e. detection of antibody binding to artificial synthetic Abeta peptide immobilized on a plastic plate. In contrast, applicants claimed method recites, in relevant part, obtaining a test sample from the subject, contacting said test sample with a tissue section containing β-amyloid plaque, determining the level of immunoreactivity of said test sample with β-amyloid plaques present in said amyloid plaque-containing tissue section. Dodel et al do not disclose such a method.

Schenk et al. teach the detection of the levels of anti-Abeta antibodies in PDAPP mice immunized with synthetic human Aβ42 utilizing ELISA assay. Schenk et al. further teach immunohistochemical analysis of the brain tissue of the immunized PDAPP mouse brain tissue. In contrast, applicants claimed method recites, in relevant part, obtaining a test sample from the subject, contacting said test sample with a tissue section containing β-amyloid plaque, determining the level of immunoreactivity of said test sample with β-amyloid plaques present in said amyloid plaque-containing tissue section. Schenk et al. do not disclose such a method and therefore do not overcome the deficiencies of Dodel et al.

Applicants maintain, therefore, that Dodel et al. in combination with Schenk et al. do not teach or suggest each and every element of applicants' invention as recited in claim one. Specifically, Dodel et al. nor Schenk et al. teach obtaining a test sample from the subject, contacting said test sample with a tissue section containing β-amyloid plaque, determining the level of immunoreactivity of said test sample with β-amyloid plaques present in said amyloid plaque-containing tissue section.

Moreover, the method of the claimed invention was a better indicator of a positive clinical outcome in a subject suffering from Alzheimer's disease and being immunized against a β-amyloid component than the conventional ELISA method for detection of Abeta antibodies. Specifically, as disclosed in the specification beginning on page 19, last paragraph, patients with high antibody titers in conventional ELISA assays of anti-Aβ antibodies, but with low levels of immunoreactivity against β-amyloid in brain tissue, as determined by the method of claim 1, did not experience beneficial clinical effects, whereas 3 patients with high levels of immunoreactivity, as determined by the method of claim 1, were protected against disease progression, regardless of their low or absent titers in the ELISA assay. These data show a dose-response relationship between the increase in serum antibodies against beta-amyloid plaques and the clinical outcome as

measured by the method of claim 1. Patients with increases in immunoreactivity levels as determined by the claimed method were essentially protected from disease progression. In contrast, no significant differences in clinical measures, cognitive performance, or neuropsychological tests were observed when ELISA titers of antibodies against Abeta peptides were used to differentiate responders from nonresponders. This difference between the method of claim 1 and ELISA scores could be related to important qualitative characteristics of the antibodies with respect to epitope recognition, affinity, and avidity of the binding reaction with beta-amyloid plaques in the physiologic brain environment. These conditions may not be mimicked adequately by preparations of synthetic Abeta on ELISA plates. Together, the data underscore the importance of using the newly described method of claim 1 for antibody analyses, and the data suggest using the method of claim 1 instead of ELISA titers for the analysis of responders. Neither Dodel et al. nor Schenk et al., alone or in combination, teach or suggest such a result.

For the reason stated above, applicants maintain that Dodel et al. (EP1172378) in view of Schenk et al. (Nature 1999) do not render obvious applicants' claimed invention.

In view of these remarks, applicants maintain that claim 1 and the claims which depend therefrom, satisfy the requirements of 35 U.S.C. §103. Accordingly, applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

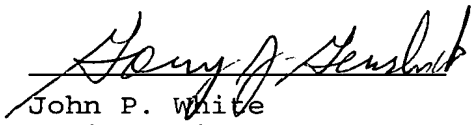
Conclusion

In view of the remarks hereinabove, applicants respectfully submit that the grounds of rejection set forth in the August 17, 2007 Office Action have been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw these grounds of rejection and allow claims 1, 3-7 and 18.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $1,050.00 three-month extension fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorney for Applicants
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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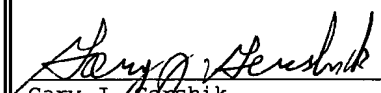

Gary J. Gershik 2/19/08
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